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JUNE 12 AND 13, 1944
ABSTRACTS OF PAPERS

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Papers Read

ENDOCRINE DISEASE AS ENCOUNTERED IN THE EXAMINATION OF 13 MILLION REGISTRANTS. *Rowntree, L. G.*, National Headquarters, Selective Service System, Washington, D. C.

No abstract.

THE ROLE OF THE LIVER IN THE METABOLISM OF SYNTHETIC ESTROGENS AND PROESTROGENS. *Segaloff, Albert* (introduced by Warren O. Nelson) Department of Anatomy, Wayne University, College of Medicine, Detroit, Michigan.

It is now generally acknowledged that the liver is a major site of inactivation for the natural estrogens. Very little such evidence is available for synthetic substances possessing estrogenic activity. Accordingly synthetic estrogens were studied by our technique of intrasplenic injection. It was found that diethylstilbestrol and hexestrol required 17 and 22 times as much, respectively, when injected into the spleen *in situ* as when injected into the transplanted spleen divorced from the portal circulation. Considerably smaller amounts of diethylstilbestrol dipropionate were required. This indicated that a considerable portion of the free compound was inactivated by the liver and that the inactivation probably proceeds through the hydroxyl groups since esterification affords protection against inactivation. In striking contrast to the behavior of the above compounds triphenylethylene, triphenylchlorethylene and 9,10-di-n-propyl-9,10-de-hydro-9,10-dihydroxy-1:2:5:6 dibenzanthracene required only one-eighth to one-fifth as much when injected into the spleen *in situ* as when injected into the spleen divorced from the portal circulation. It thus appears that the systemic activation proposed by Emmens for such proestrogens as the last three compounds takes place in the liver.

THE INFLUENCE OF HORMONES UPON THE CHEMIAL COMPOSITION OF THE BRAIN. *Weil, Arthur.* Northwestern University, Chicago, Illinois.

The paper is concerned with the effect of sex hormones, the adrenal gland and the hypophysis upon the phospholipid content of the brain of white rats. It had been shown previously that both hyper- and hypothyroidism do not change the phospholipid content qualitatively.—Removal of the gonads changes the different chemical constitution of the male and female brain to a more neutral intermediate level. Injections of homologous sex hormones (testosterone propionate and α-

estradiol benzoate) into immature rats have no qualitative effect upon the chemistry of the brain; however, injections of heterologous sex hormones change the male brain into a female one and vice versa. This effect may be obtained in both normal and castrated rats. Following adrenalectomy there is a considerable increase in the size of both male and female brains with a proportional increase in the amount of the different lipid fractions, but without qualitative changes. Hypophysectomy affects the male brain slightly more than the female brain and leads to a mild increase in the amount of phospholipids and their phosphorus content.

SUSTAINED REMISSION OF HYPERTHYROIDISM AFTER THIOURACIL THERAPY. *Astwood, E. B.* From the Medical Clinic of the Peter Bent Brigham Hospital and the Departments of Medicine and Pharmacology, Harvard Medical School, Boston, Massachusetts.

Shortly after hyperthyroidism had been controlled with thiouracil the withdrawal of medication in nine instances was followed by a return of symptoms and a rise in metabolic rate within 7 to 45 days. However, when treatment was not discontinued until metabolic equilibrium had been maintained with thiouracil for 6 to 9 months, continued remissions occurred. Of eleven such patients, ten have been observed closely for longer than three months and have exhibited no evidence of recurrence. In the event of subsequent relapse, treatment with a maintenance dose of thiouracil could be resumed as soon as symptoms are noted. Before thiouracil was withdrawn, all patients had been free of symptoms on a small maintenance dose and those with large goiters exhibited a decrease in the size of the gland and disappearance of the bruit. These signs were taken to imply that spontaneous improvement had begun.

METABOLIC EFFECTS OF THIOURACIL IN GRAVES' DISEASE. *Sloan, Margaret H.* and *Ephraim Shorr.* From the Russell Sage Institute of Pathology, The Department of Medicine, Cornell University Medical College and The New York Hospital, New York City.

A study was made of the effect of thiouracil on the disturbances in calcium, phosphorus, nitrogen, creatine-creatinine, cholesterol and 17-ketosteroid metabolism in patients with Graves' disease under carefully controlled conditions. The findings were correlated with other indices of thyroid activity. All these various metabolic derangements were corrected by the administration of thiouracil just as occurs after subtotal thyroidectomy or in iodine remission. The remissions produced by this new drug are, therefore, physiologic.

EXPERIMENTAL AND CLINICAL STUDIES ON THE ACTION OF THIOUREA AND THIOURACIL. *Paschkis, K. E., A. Cantarow* and *A. E. Rakoff.* Endocrine Clinic, Jefferson Medical College and Hospital, Philadelphia, Pennsylvania.

The relative potency of thiourea and of thiouracil inhibiting enzyme systems *in vitro* was studied. In experiments on rats it was attempted to suppress overactivity of the anterior pituitary associated with the suppression of formation of thyroid hormone. The clinical effect of treatment of thyrotoxicosis with thiourea and thiouracil was studied in 20 cases. Establishment of a "permanent maintenance dosage" was attempted rather than intermittent treatment. Four cases in which surgery was contraindicated are of particular interest. Special attention was paid to the occurrence of toxic manifestations.

THE EFFECT OF THIOURACIL ON THE COLLECTION AND SECRETION OF RADIOACTIVE IODINE BY THE THYROID. *Larson, Roger, F. R. Keating, Jr., Rulon W. Rawson* and *Wendell Peacock.* From the Institute of Experimental Medicine, The Mayo Foundation, Graduate School, University of Minnesota (Doctor Larson), the Division of Medicine, The Mayo Clinic (Doctor Keating), Rochester, Minne-

sota, the Thyroid Clinic of the Massachusetts General Hospital (Doctor Rawson) and the Radiation Center, Massachusetts Institute of Technology (Doctor Peacock), Boston, Massachusetts.

An artificially radioactive isotope of iodine having a half-life of eight days was injected in chicks. The proportion of the substance collected by the thyroid and the rate at which that previously collected was lost from the thyroid were determined. The glands were digested in alkali and their content of radioactive iodine measured with a Geiger counter. The weight of the thyroid gland and the mean height of acinar cells were also studied. Varying doses of thiouracil injected or administered in the drinking water produced a striking decrease in the collection of radioactive iodine by the thyroid. This effect appeared within an hour after administration of thiouracil and had largely worn off in less than 24 hours. The drug did not alter the rate at which iodine previously stored in the gland was lost. Histologic changes did not appear until thiouracil had been administered for several days. The ability of thyroid glands made goitrous by prolonged administration of thiouracil to collect radioactive iodine also was diminished but this effect wore off rapidly when the drug was withdrawn.

THE ABSORPTION, DISTRIBUTION AND EXCRETION OF THIOURACIL AND THE IMPORTANCE OF THESE FACTORS IN THE TREATMENT OF THYROTOXICOSIS. *Williams, Robert H.* and *Howard M. Clute.* Thorndike Memorial Laboratory, The Boston City Hospital, Boston, Massachusetts.

Thiouracil is rapidly absorbed from the gastro-intestinal tract and is distributed throughout all of the body tissues and fluids. Tissues storing the largest amount are the pituitary, thyroid, adrenals and bone marrow; the skin, muscle and liver contain the smallest amount. Thiouracil in the blood is largely bound to protein, the cells possessing several times as much as the plasma. Most of the tissues of the body and also the gastro-intestinal contents possess the capacity to destroy thiouracil. About one-third of the ingested drug is excreted as such in the urine, but none in the feces. These observations, together with the clinical experience in the treatment of 105 thyrotoxic patients indicate that it is better to give frequent small doses throughout the day than one or two larger doses. If more than 0.4 gm. daily of the drug is administered, the concentration in the blood increases only slightly in proportion to the dosage. The concentration of thiouracil in the thyroid glands of 24 thyrotoxic patients showed no correlation with the clinical response of the patient, with the histological alterations in the gland, nor with its content of thyroxin iodine.

THE EFFECT OF THIOURACIL AND OF POTASSIUM THIOCYANATE ON THE COLLECTION OF RADIOACTIVE IODINE BY THE THYROIDS OF ANIMALS AND MAN. *Rawson, Rulon W., Ruth E. Cortell, Wendell Peacock* and *J. H. Means.* From the Thyroid Clinic of the Massachusetts General Hospital, Boston, Massachusetts and the Radioactivity Center Department of Physics, Massachusetts Institute of Technology, Cambridge, Massachusetts.

The effects of iodine-inhibited, and iodine-resistant goitrogens on the thyroid's collection of iodine have been determined. Experimental goiters produced by potassium thiocyanate, an iodine-inhibited goitrogen, were found to collect 153% more of the administered radioactive iodine than did the thyroids of control animals. Goiters produced by the administration of thiouracil, an iodine-resistant goitrogen, though extremely hyperplastic, collected less than 18% as much of the administered iodine than did the thyroids of control animals. In a similar series of experiments the avidity for iodine of rat thyroids made goitrous by thiouracil two, five, ten and twenty days after stopping the administration of the drug was determined to learn the rate of recovery from the block produced by this agent. Since

thiouracil goiters can be prevented by thyroxine, the thyroid's avidity for iodine was determined in rats treated with thiouracil and thyroxine. Thyrotoxic patients following preparation for thyroidectomy with thiouracil were found to excrete in the urine most of the administered radio-active iodine. Very little of the iodine was demonstrated in the thyroids removed at operation. Patients made goitrous by potassium thiocyanate administered in treatment of hypertension excreted very little of the administered iodine.

ESTROGEN ACTIVITY IN THE EVISCERATED RAT. *Szego, Clara M., Sidney Roberts,* and *Leo T. Samuels.* Division of General Physiology and Physiological Chemistry, Department of Physiology, University of Minnesota Medical School, Minneapolis, Minnesota.

Doses of estrone and α-estradiol sufficient to cause maximal response in three-month-old female rats two weeks after ovariectomy were ineffective in similarly-prepared eviscerated animals (kidneys intact). The index of estrogen activity employed was the increase in uterine water content. Responses to α-estradiol were noted in control animals autopsied ten hours after administration of $0.2\gamma/100$ gm. body weight subcutaneously in sesame oil, five hours after 0.2γ intravenously in saline, and six hours after 0.5γ injected into the cervical lumen. No response was obtained in eviscerates with 0.2–0.5γ α-estradiol or estrone over periods varying from three to twenty-four hours after the first of divided dosages by combined routes. Large doses of intravenously-injected α-estradiol were inactive in eviscerated rats previously maintained on a diet containing 1% desiccated thyroid, even though the basal metabolic rates five hours after evisceration were in the normal range. Non-eviscerated, thyroid-treated animals (B.M.R., +50%) responded normally. These results indicated that removal of the viscera interfered with uterine response to estrogen. Additional experiments have been carried out employing gut removal alone. Moreover, evisceration has been performed at short intervals *after* estrogen administration.

EFFECTS OF EXOGENOUS SEX HORMONES ON THE GONADS OF SPARROWS. *Pfeiffer, Carroll A.* Department of Anatomy, Yale University School of Medicine, New Haven, Conn.

Administration of 0.25 mg. of testosterone propionate daily to adult male sparrows at the beginning of the breeding season markedly increased the size of the testes within two weeks and maintained maximum development for at least 80 days. If treatment was stopped after two weeks the testes regressed to their former size or smaller within a week but could be enlarged again, although not as markedly. Eventually they regressed to the non-breeding condition despite continued treatment. When the same dose of androgen was given to young juvenal birds whose testes were readily stimulated by gonadotrophins but whose pituitaries were unresponsive, enlargement of the testis did not occur. Androgen stimulated, although to a less degree, the ovaries of mature but not juvenal females. In both types of females the oviducts became enlarged, but less so in juvenals, indicating that the greater development in adult females was due to estrogen released by the stimulated ovaries, since at either age the oviducts had about the same sensitivity to injected estrogen. Estrogens inhibited the normal enlargement of both testes and ovaries. Either hormone injected in oil slightly inhibited PMS-induced testicular enlargement, presumably because the unabsorbed oil interfered with absorption of the PMS.

DEPENDENCE OF OESTROUS CYCLES IN RATS ON VITAMIN D. *Richter, Curt P.* and *Katherine K. Rice.* Psychobiological Laboratory, Phipps Psychiatric Clinic, Johns Hopkins Hospital, Baltimore, Maryland.

In preliminary studies on small numbers of rats it was found that female rats given access to only yellow corn and water for several months were inactive and underweight, had poor appetites and remained in a constant dioestrous condition.

When given access to cod-liver oil, or to crystalline vitamin D_3 in cotton-seed oil, or exposed to ultraviolet rays, the deficiency was corrected almost at once. Within a day they became more active, and had increased appetites, and within 4 days cornified cells appeared in the vaginal smears. Within 15 days the animals often showed a full return to all normal levels. These observations have now been confirmed on larger groups of rats with histological sections of ovaries and uteri and also experiments on reproductive activity. These experiments demonstrate the close dependence of the reproductive function on vitamin D.

A Urine Color Reaction for Human Pregnancy. *Guterman, Henry S.* (introduced by Samuel Soskin). From the Department of Metabolism and Endocrinology, Michael Reese Hospital, Chicago, Illinois.

Pregnandiol excretion begins at approximately the time of ovulation, increases through the second half of the menstrual cycle, and ceases prior to the onset of the flow unless fertilization has occurred. In the latter event pregnandiol is excreted in increasing amounts as normal pregnancy progresses. Based upon these facts, a simple chemical procedure for the diagnosis of pregnancy has been devised. By modifying Astwood's and Jones' (J. Biol. Chem., *137:* 397, 1941) method for the extraction of pregnandiol from urine and Talbot's (J. Clin. Endocrinol., *1:* 668, 1941) colorimetric determination of the substance, it was possible to obtain a qualitative color reaction which agrees with the results of the Friedman rabbit test. One hundred cc. of the first morning specimen are used and the test is completed in three hours. Several tests can be carried out simultaneously. This procedure has the following advantages: (1) rapidity (3 hours); (2) does not involve use of animals; (3) becomes positive earlier than the Friedman test; (4) in conditions other than normal pregnancy, in which the prolan excretion is raised sufficiently to give a positive Friedman reaction, the pregnandiol test is negative.

Menorrhagia—Its Control by Prolactin. *Kupperman, Herbert S., Paul Fried* and *L. Q. Hair.* Department of Experimental Medicine, University of Georgia School of Medicine, Augusta, Georgia.

Menorrhagia, either functional or organic, was favorably influenced by administration of lactogenic preparations (pituitary). Menorrhagia associated with uterine fibroids, cystic ovaries or chronic pelvic inflammatory disease was suppressed by administration of prolactin in the majority of patients. Those patients, however, in the latter two cateogires, were more resistant to therapy. Normal cyclic bleeding followed cessation of prolactin therapy in many of the patients receiving one or more courses of treatment. This permanence, or semi-permanence, in the effect of prolactin afforded a sufficient interval to enable the patient to undergo a more strenuous régime to correct the underlying cause of the excessive uterine bleeding. Some success was obtained in mitigating dysmenorrhea by prolactin therapy when it was associated with excessive uterine bleeding. In addition, the signs and symptoms of threatened abortion were alleviated by administering prolactin to 3 of 6 patients with histories of previous abortions. Administration of lactogenic preparations to normally cyclic women had no appreciable effect upon the length of cycle, menstrual bleeding or morphological appearance of the endometrium. The effectiveness of lactogenic hormone in controlling uterine bleeding is probably linked up with its uteotrophic properties. In view of the innocuous effect of prolactin upon the normal menstrual cycle and corrective action in metropathic menorrhagia, its use is advocated in the control of excessive uterine bleeding.

The Vaginal Smear in the Diagnosis of Cancer of the Uterus. *Fremont-Smith, Maurice.* Vincent Memorial Laboratory, Mass. General Hospital. Boston, Massachusetts.

Vaginal smears from approximately 800 cases have been examined. Of these,

634 smears were negative, 117 positive for cancer (cervix or body) and 8 suspicious (no diagnosis possible). In the case of 6 positive smears a fixed tissue diagnosis of cancer has not been established (unfinished cases). 22 diagnoses are listed as mistakes (positive smear with negative fixed tissue diagnosis, or negative smear in cases proven to have cancer). In 3 cases cervical carcinoma *in situ* was diagnosed by vaginal smear. Cervical biopsy in one of these two was indeterminate; cancer was found by section. 6 unsuspected cancers of the cervix were diagnosed by vaginal smear, and confirmed by fixed tissue section. The technique of collection and staining is described.

PERLINGUAL ABSORPTION OF PROGESTERONE AND ANHYDROHYDROXYPROGESTERONE. *Greenblatt, Robert B.* Southeastern Medical Center, Oatland Island, Savannah, Georgia.

Proof for the sublingual absorption of such steroids as estradiol, methyl testosterone or anhydrohydroxyprogesterone has not been convincing inasmuch as part of these preparations may be swallowed. On the other hand, progesterone is inactivated by ingestion. If it can be shown that progesterone is effective when applied sublingually, it would afford proof that the other steroids are also absorbed by way of the oral mucosa. Observations were made on 62 patients following 133 courses of therapy. Sublingually anhydrohydroxyprogesterone was used in 92 courses and progesterone in 41 courses. Endometrial biopsies were taken when feasible prior to and after administration of a course of therapy. The criteria for effective absorption of each preparation were: the induction of "progesterone withdrawal bleeding" in amenorrheic patients; the effective arrest of menorrhagia six to ten days after withdrawal of the drug, i.e., "arrest of bleeding according to plan." The effectual absorption of these preparations was surmised from the beneficial effects noted in patients with mastodynia, premenstrual tension, certain patients with dysmenorrhea, as well as its varying effect on sexual libido. Occasionally in lieu of the withdrawal bleeding that was expected following sublingual medication, the patients experienced molimina, breast turgidity or uterine cramps.

THE EXCRETION OF SODIUM PREGNANEDIOL GLUCURONIDATE IN THE URINE FOLLOWING THE ORAL ADMINISTRATION OF ANHYDROHYDROXYPROGESTERONE AND PROGESTERONE TO PATIENTS WITH SECONDARY AMENORRHEA. *Allen, Willard M., Ellenmae Viergiver,* and *Samuel D. Soule,* Washington University School of Medicine, St. Louis, Missouri.

Anhydrohydroxy-progesterone or progesterone was given orally in doses from 200 to 500 mg. per day for a period of from one to six days to several patients with secondary amenorrhea. The urine was collected daily under butyl alcohol for a period of two to three days before therapy, during therapy, and for a period of from four to seven days following cessation of therapy. The urine was then extracted with butyl alcohol and the sodium pregnanediol glucuronidate determined by the method of Viergiver and Allen. In all cases there was a considerable increase in the amount of sodium pregnanediol glucuronidate excreted in the urine while the preparations were being taken orally. The amount recovered in the urine varied from six to twelve per cent of the theoretical amount. The excretion of ketosteroids was also determined but in no case was there any indication that an increased amount of ketosteroid was excreted while the two preparations were being taken orally. Estrogens were likewise studied in the urine by a modification of the Kober method but no estrogen was measurable by this method either before, during or after therapy.

OBSERVATIONS ON THE EXPERIMENTAL USE OF GONADOTROPIC EXTRACTS IN THE HUMAN FEMALE. *Davis, M. Edward* and *Arthur Hellbaum.* From the Department of Obstetrics and Gynecology, the University of Chicago, and the Department of Pharmacology, the University of Oklahoma, Oklahoma.

During the past year gonadotropic extracts have been made available for experimental use in man. These extracts have been brought to a high degree of purity by the elimination of much of the extraneous substances. Fractionated extracts have been found to contain F.S.H. only, whereas unfractionated extracts contain L.H. as well as F.S.H. The efficacy of these pituitary extracts in gonadal stimulation and the production of ovulation has been demonstrated in the rat, the sheep, and the cow. These extracts were tested for reactions when administered intramuscularly and intravenously. Earlier samples produced some undesirable symptoms but these have become less common. Considerable evidence has been accumulated previously concerning the histologic appearance of the ovary during the immediate postpartum period. The absence of normal follicle activity suggested this period in the life cycle of the ovary as ideal for the study of gonadotropin effects. The changes induced by these pituitary preparations on the human ovary in the immediate postpartum period were studied. In most patients an ovary was removed for histologic study. Follicle growth of physiologic and pathologic proportions was induced. It was not possible to produce ovulation although it was felt that this goal can be achieved by continued observations. It is possible that the human ovary in the immediate postpartum period is not normally receptive to gonadotropic stimulation.

THE CAUSES, DIAGNOSIS AND TREATMENT OF VARIOUS TYPES OF SEXUAL INFANTILISM IN FEMALES. *Wilkins, Lawson.* Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Sexual infantilism in females may be due to: (A) primary ovarian deficiency; (B) ovarian deficiency secondary to a lack of secretion of pituitary gonadotropin. In the first group are cases due to (1) ovarian agenesis; (2) destruction or removal of the ovaries before puberty. In the second are cases of (1) pituitary dwarfism; (2) Froehlich's syndrome; (3) specific deficiency of pituitary gonadotropin. The clinical findings in these various conditions are illustrated and discussed. The value of diagnostic studies, including the assay of F.S.H. in the urine and the 17-ketosteroids is considered. The importance of exploratory laparotomy or peritoneoscopy is stressed. Indications for various types of treatment are discussed and the shortcomings of gonadotropic therapy are pointed out. Plans of treatment with estrogen and progestin and with androgen in proper cases are described. A case is reported of a patient with pituitary infantilism who was successfully treated.

OVARIAN FOLLICLES IN NORMALLY CYCLIC AND PERSISTENT-ESTRUS RATS. *Jeffers, Katherine R.* Duke University, Durham, North Carolina.

Counts and measurements were made of growing and degenerating follicles in ovaries of control rats and rats which had been in estrus for prolonged periods of time. The sectioned ovaries were from animals of the DA strain. The controls were 1) rats in estrus with enlarged follicles prior to ovulation; 2) rats in estrus with recently formed corpora lutea; and 3) pregnant (20 days) rats with large functional corpora lutea. It was found that the average number of follicles per ovary increases after ovulation, with growth taking place in all sizes of follicles up to 500 microns in diameter. The increase is most marked in early stages of growth. An increase in follicles 200–500 microns in diameter occurs in late pregnancy. Degeneration of follicles is more marked after ovulation. Two groups of animals with persistent estrus were studied: one nonpregnant and the other pregnant. The average number of follicles in the persistent-estrus animals is less than half that of the controls. Growth at all stages is slower, apparently, although very large vesicular follicles (up to 800 microns in diameter) occur in the non-pregnant rats.

RELATION BETWEEN LIGHT-DARK RHYTHMS AND HOUR OF LAY OF EGGS EXPERIMENTALLY RETAINED IN THE HEN. *Rothchild, Irving,* and *R. M. Fraps,* Bureau of Animal Industry, U. S. Dept. of Agriculture, Beltsville, Maryland.

The present authors have demonstrated that removal of the avian ruptured ovarian follicle results in retention of the oviducal egg for 1 to 7 days beyond expected time of lay (in press). We have since found that removal of all follicles in the phase of rapid growth together with the ruptured follicle results generally in more uniform retention of eggs (10–28 hours beyond expected time of lay). Further, most such retained eggs were laid during normally lighted hours (6:00 A.M.–8:00 P.M.), the peak of the distribution curve falling between 1:00 and 3:00 P.M., or 7 to 9 hours following onset of light. In similarly operated birds placed under reversed lighting conditions (lights 4:00 P.M.–6:00 A.M.) immediately following operation, the peak in the distribution curve for hour of lay fell between 11:00 P.M. and 2:00 A.M., or 7 to 11 hours following onset of light. Most eggs were retained either 10–18 or 28–36 hours, thus being laid during either of two successive lighted periods. Since the hour of (delayed) lay in these birds conforms to alternations in light and darkness in the complete absence of the normal regulating mechanism, the participation of an extra-ovarian agency, possibly the pituitary, seems indicated in the process of avian oviposition.

THE ROLE OF THE PITUITARY IN TOXIC GOITER. *Thompson, Willard O.* and *Phebe K. Thompson.* University of Illinois College of Medicine, Chicago, Illinois.

Ever since the demonstration of the thyrotropic activity of the pituitary there has been great interest in its role in toxic goiter. During the past several years we have observed the effect of irradiation of the pituitary in 38 patients with toxic goiter. In 7 of them the metabolism dropped permanently to within normal limits. In 16 a temporary reduction in metabolism of from 15 to 52 points was observed. In 15 patients there was no change. These observations appear to support the hypothesis that in some patients with toxic goiter the anterior lobe of the pituitary stimulates the thyroid to overactivity. While the results of treatment with thiourea, thiouracil and radioactive iodine are very important, these materials do not appear to attack the underlying cause of the disease.

GROWTH AND TREATMENT OF DWARFS AND GIANTS. *Bayer, Leona M.* Stanford University School of Medicine, San Francisco, California.

Sixteen presumably hypopituitary dwarfs and four hyperpituitary giants were followed from one to 13 years through periods of treatment and control. Data are analyzed particularly from the longitudinal viewpoint. Growth of dwarfs and giants shows contrasts similar to differences between early-maturing and late-maturing normals. In *growth rate* dwarfs tend to late adolescent spurts, sometimes of considerable magnitude; giants to early spurts. In *stature* and *skeletal development* dwarfs fall further behind normal before adolescence, recover gradually thereafter. Inversely, giants show preadolescent acceleration, with subsequent return toward normal. When *sitting height-stature ratios* are noted, dwarfs tend to be short legged; giants may be long legged before adolescence, short or medium legged afterwards. *Basal metabolic rates* have a surprising distribution; many dwarfs have rates above normal; giants below normal. Contrastingly, *intelligence quotients* tend to be low in dwarfs, high in giants. Observations include periods of treatment with thyroid, growth hormone, sex hormones, and their combinations. During adolescence the inherent growth tendency often supersedes effects of any treatment. In dwarfs, thyroid periods most consistently show stimulation of all phases of growth. With other extracts, especially sex hormones, a few striking improvements encourage continued trial.

HYPOPITUITARISM ASSOCIATED WITH EPILEPSY FOLLOWING HEAD INJURY: REPORT OF TWO CASES. *Lerman, Jacob* and *James H. Means.* Massachusetts General Hospital, Boston, Massachusetts.

Two patients with hypopituitarism and epilepsy were encountered. The first, a male of 46, was shot through the head at the age of 15. The bullet entered the left

orbit, traversed the pituitary fossa and lodged behind the posterior clinoids. Growth and development ceased and gradually epileptiform seizures supervened. The second, a male of 48, was injured in World War I by the explosion of a shell. He received several shrapnel wounds and was knocked unconscious. He, also, developed epileptic seizures. They both presented characteristic clinical and laboratory evidence of hypopituitarism. They differed only with respect to stature. The first patient was a partial dwarf; the second, having received his injury at the age of 22, was of normal size. Diagnosis and specific therapy are discussed.

CRETINOUS PITUITARISM. *Dunn, Charles W.* Philadelphia, Pennsylvania.

Myxedema can result from primary deficiency of pituitary thyrotropic secretion. The condition can develop in infancy and resembles clinically infantile myxedema due to primary fetal thyroid deficiency. The latter is characterized by retarded fetal development. Five cases of cretinous pituitarism are reported in all of which earlier diagnosis of thyrogenic cretinism had been made. Thyroid treatment had evoked toxic symptoms. Mental advancement disproportionate to administered thyroid had occurred but statural and sexual development had halted at from 10 to 14 years. The treatment should be addressed to the pituitary factor in the disorder.

ON THE RENOTROPIC ACTION OF AN ANTERIOR PITUITARY EXTRACT. *Selye, Hans* and *Kai Nielsen.* Department of Anatomy, McGill University, Montreal, Canada.

Previous experiments showed that various steroids stimulate the growth of kidney tissue. Since extracts of the anterior lobe of the hypophysis also cause renal enlargement, it was felt that the histological changes caused by anterior pituitary extracts should be compared with those elicited by steroids. Unilaterally nephrectomized female rats, having an initial average weight of 55 gm., were divided into two groups. Group I received no further treatment. Group II received two daily subcutaneous injections of a crude alkaline beef pituitary extract. After two months of treatment, when all animals were killed, the average body weight of the treated rats was 205 gm. and the average kidney weight 2150 mg. In the control group the corresponding average weights were 157 gm. and 1222 mg. respectively. It appears that the compensatory hypertrophy of the kidney remnant is more intensely stimulated by the extract than could be accounted for by its body-growth-promoting action. Histologically both the glomeruli and the tubules of the kidneys were enlarged but otherwise apparently normal. The liver weight was also markedly increased by this extract (14.3 gm. in the treated, 7.7 gm. in the controls). It is concluded that certain anterior lobe extracts selectively stimulate renal and hepatic growth. In the mouse, combined administration of anterior lobe extract and testosterone enlarged the kidney up to 5 times its normal weight.

DO MASSIVE DOSES OF ESTROGEN DEPRESS THE HUMAN PITUITARY AND THUS THE OVARY? *Abarbanel, A. R.* Department of Obstetrics and Gynecology, George Washington University School of Medicine, Washington, D. C.

A series of patients with excessive functional meno-metrorrhagia bleeding from endometria showing cystic glandular hyperplasia were given from 600 to 1200 mg. of oral diethystilbestrol over a period of 6–12 weeks. Endometrial biopsies at weekly or bi-weekly intervals disclosed a marked proliferative effect during the course of therapy. Within 5–10 days after the estrogen was stopped, estrogen-deprivation bleeding ensued. In each case biopsies taken 3–4 weeks later showed a strong secretory pattern and in several instances, a marked decidual reaction. In 10 of 12 such cases, menses became rhythmically cyclic and normal in amount, while follow-up premenstrual endometrial biopsies revealed a secretory pattern. These results are in harmony with the cytological studies of A. Sevringhaus, who

postulated that estrogen in small doses stimulated increased functional activity of the basophiles of the anterior pituitary (increase in mitochondria and Golgi apparatus and degranulation). Larger doses stimulated, in addition, the eosinophiles of the anterior hypophysis in a similar manner, releasing the luteinizing fraction. The evidence presented by these studies tends to confirm the second part of A. Sevringhaus' postulates. Further, it is in keeping with the experimental evidence of Hohlweg and Westman, in inducing ovulation and/or luteinization in young female rats with large doses of estrogen over a short perilod of time. Moreover, the failure of large doses of estrogen seemingly to depress the anterior pituitary is in line with the author's previous reports on the effect of estrogen on lactation in the human.

CHANGES IN THE RESPIRATORY QUOTIENT ASSOCIATED WITH DEVELOPMENT OF EXPERIMENTALLY PRODUCED OBESITY IN THE MONKEY (MACACA MULATTA). *Brooks, Chandler McC.* and *E. M. Bridge.* Departments of Physiology and Pediatrics, Johns Hopkins Univ. School of Medicine, Baltimore, Maryland.

Experimentally-produced lesions involving the suprachiasmatic areas and the tuberal region of the hypothalamus cause obesity in monkeys (Brooks, Lambert and Bard, 1942). Metabolic studies were made on three monkeys before and after such an operation, on a fourth during the static phase of obesity, and on a fifth normal monkey. One monkey was fed an excess of food after operation, one was given the same amount received before operation and one was restricted to its daily pre-operative intake. In this latter case the food was divided into four equal parts which were given at 9:00 A.M., 12:00 P.M., 3:00 P.M. and 6:00 P.M. The basal respiratory quotient was found to be somewhat above normal during the post-operative period of rapid weight gain. Furthermore, ingestion of food produced a rise in R. Q. (.81–.85 to 1.04–1.12 uncorrected) far exceeding that which occurred, after ingestion of similar quantities of food, in the normal control monkey and in these same animals before operation. In the monkey which had long been obese and in the three recently prepared animals after they had attained a static phase of obesity, the change in R. Q. after feeding was less marked (.82–.85 to .91–.95 uncorrected). The duration of R. Q. changes appeared to be related to the quantity of food ingested. The hypothesis suggested by these results is that, in the monkey, following this type of hypothalamic lesion a high proportion of food ingested is converted to fat. After obesity has been fully attained changes occur which diminish this tendency to convert ingested food to fat.

IS OBESITY ENDOCRINE OR WHY FAT PEOPLE EAT. *Richardson, Henry B.* From the Department of Medicine, the New York Hospital, and Cornell University Medical College, New York City.

Endocrinology in the popular view is the modern magic, and is supposed to supply both the explanation and the cure of obesity. Contrary to popular view not all endocrine cases are obese nor do all fat people have endocrine disturbances. In the great majority of cases no endocrine defect can be demonstrated and no consistent disturbances in the basal metabolism, sugar tolerance or specific dynamic action have been observed. It is not known whether the obese person lays down fat with any more facility than the normal or has any more difficulty in oxidizing it. An important factor is motivation in eating and this is extremely varied. The fundamental understanding of the motives requires a knowledge of the life history as to the family during childhood, the development of maturity, the adult situation and the personality reactions. With these data it is possible to understand the motivations in eating and being fat, not only the expressed motivations, but some of the symbolic meaning and psychological gain of the obesity. These observations throw more light on the etiology of obesity than all the present laboratory tests. The suc-

cessful reduction of weight depends on the degree to which the psychological factors are understood by the patient or utilized in the treatment by the doctor.

CYTOLOGICAL CHANGES IN THE PARATHYROID GLANDS FOLLOWING BILATERAL NEPHRECTOMY OR LIGATION OF THE URETERS. *Baker, Burton L.* Department of Anatomy, University of Michigan, Ann Arbor, Michigan.

The parathyroid glands are known to enlarge as a result of renal insufficiency and it has been suggested that in this condition, they are functionally hyperactive. It was thought that bilateral nephrectomy or ureteral ligation might alter the structure of the parathyroid cells and thus aid in the elucidation of their cytology. One of these operations was performed on 23 adult rats with 12 litter-mates serving as controls. This report is concerned primarily with changes observed in glands prepared by the Nassonov-Kolatschev technique. The cells of the normal rat parathyroid prepared by this method vary considerably in size, density of cytoplasm and form of the Golgi apparatus. The operative procedures employed caused the appearance of many large cells whose Golgi apparatus was located on only one side of the nucleus. It tended to possess a more spherical contour than in the normal glands and was definitely enlarged. Dark osmiophilic cells, which have been reported to be more numerous in rats subjected to low calcium and low phosphorus diets, were not significantly increased in number. The changes observed were independent of sex; they were similar after both types of operation and, hence, not dependent on the presence of renal tissue.

ACTION OF ESTROGEN ON PLASMA CALCIUM AND ENDOSTEAL BONE FORMATION IN PARATHYROIDECTOMIZED PIGEONS. *Riddle, Oscar* and *Vita M. Rauch.* Carnegie Institution, Department of Genetics, Cold Spring Harbor, New York.

In the race (Carneau) chiefly used, the four parathyroids are normally separated completely from the thyroids; parathyroidectomy, as performed here by G. C. Smith, avoids injury to thyroids. In operated birds of both sexes plasma calcium quickly decreased from approximately 9.0 to 6.1 mg. % (19 females) or 6.0 mg. % (20 males). In young birds (2–4 mo.) estradiol benzoate, 0.5 mg. daily for 4 days, increased plasma calcium to 26.0 mg. in 16 normal and to 20.9 mg. in 18 parathyroidectomized birds; macroscopically the femurs of both groups showed no more than traces (grade 1) of transformation of marrow to bone. Six older (4 + mo.) males gave similar results; in one of six older operated females the entire marrow cavity was replaced by bone (grade 4). Dosage over 15 days, 0.25 mg. daily, produced rather similar increases of plasma calcium in normal (to 25.0 mg. for 18) and parathyroidectomized birds (to 19.4 mg. for 12). Ossification of grades 2 and 3 predominated in younger birds, grades 3 and 4 in older birds, both operated and intact. The more characteristic actions of estrogens on blood calcium and bone in pigeons occur in the absence of the parathyroids.

TENSILE STRENGTH OF TISSUES AS INFLUENCED BY MALE SEX HORMONE. *Herrick, Earl H.* Elizabeth Clay Howald Fellow, Ohio State University, Columbus, Ohio.

Recognizing that young fowls treated with male sex hormone (testosterone propionate) developed skin that was more than normally resistant to tearing, measurements were made to determine the degree of this condition. Apparatus was designed to measure the breaking strength of selected tissues. Samples of skin from young fowls treated with 50 mg. of male sex hormone showed nearly 100 per cent greater tensile strength than like samples from untreated birds. The gastrocnemius muscle from the leg broke at 41 per cent greater pull in the treated than in normal fowl. The total wing muscles from the upper part of the wing were 45 per cent stronger in the treated than untreated birds. Histological conditions were studied.

THE HORMONAL REGULATION OF THE THERMO-REGULATORY FUNCTION OF THE SCROTUM. *Andrews, Frederick N.* Purdue University Agricultural Experiment Station, Lafayette, Ind.

Experiments carried out by the author and coworkers have shown that in the rat, ram, bull and boar there is a relationship between the development of the testis and the production of spermatozoa and the ability of the scrotum to respond, by contraction and relaxation, to changes in environmental temperature. When these species of animals were castrated prior to sexual maturity the scrotum failed to develop its thermo-regulatory function and if gonadectomy was performed after sexual maturity the thermo-regulatory function was lost. Studies on 64 sexually mature male albino rats showed that significant decreases in seminal-vesicle and scrotal-sac weights, and in the height of scrotal contraction occurred during the first, second and fourth weeks after castration, respectively. Coefficients of correlation of 0.915 between scrotal-contraction height and scrotal-sac weight, of 0.801 between scrotal-contraction height and seminal-vesicle weight, and of 0.843 between weights of the scrotal sacs and seminal vesicles were demonstrated. Fifty male rats were castrated at 35 days of age and injected with 0.5 mg. of testosterone propionate daily for periods of from 7 to 21 days beginning on the 90th day of age. A second group of 50 rats was castrated at 90 days of age and injected immediately with 0.5 mg. of testosterone propionate daily for from 7 to 21 days. Significant increases in height of scrotal contraction and weights of the scrotal sacs and seminal vesicles were obtained in rats castrated at 35 days of age and subsequently injected with testosterone. The injection of testosterone into sexually mature rats following castration on the 90th day of age adequately maintained scrotal sac weight and significantly increased seminal vesicle weight and the contractility of the scrotum. It is concluded that the development and maintenance of the thermo-regulatory function of the scrotum is dependent upon the testicular hormone.

THE EFFECT OF CASTRATION AND TESTOSTERONE PROPIONATE ADMINISTRATION ON THE PHOSPHORUS METABOLISM OF THE PELVES AND FEMURS OF THE MOUSE AS DETERMINED BY RADIOACTIVE PHOSPHORUS STUDIES. *Fox, R. P.* and *C. D. Kochakian.* Department of Vital Economics, University of Rochester, Rochester, New York.

Mice of the Murray-Little dba strain were divided into four groups: a) normal, b) castrate, c) normal implanted with pellet of testosterone propionate, d) castrate implanted with pellet of testosterone propionate. They were castrated and implanted at one month of age. Animals from each group were decapitated after 5, 7, 9 months. Twenty-four hours before autopsy radioactive phosphorus was injected intraperitoneally as the disodium phosphate. After fat extraction and glycol ashing, the uptake of P^{32} by the femurs and pelves was measured in the usual manner. The femurs and pelves of the castrated contained more radioactive phosphorus than those of the normal mice, whereas the femurs of the treated showed values similar to those of the normal mice. These effects were found at 5, 7 and 9 months. The femurs and pelves of the castrated mice were longer than those of the normals, while the latter, in turn, were longer than those of the treated animals. There was no difference in either ash content or calcium and phosphorus content as a result of castration or hormone administration.

METABOLISM OF TESTOSTERONE BY LIVER AND OTHER TISSUES IN VITRO. *Samuels, Leo T.* From the Division of Physiological Chemistry. Department of Physiology, University of Minnesota Medical School, Minneapolis, Minnesota.

The metabolism of testosterone when incubated with minces of liver and other tissues has been studied, using the colorimetric reaction of Koenig, *et al.* (1941). Spectrophotometric methods have been used to identify the products resulting

from alterations in the testosterone molecule. Testosterone is destroyed by normal adult rat liver mince at an average rate of 0.125 mg. per gm. tissue per hour. An atmosphere of nitrogen, or the presence of either 0.05M sodium fluoride or 0.01 M sodium cyanide inhibits the reaction.

The reaction appears to occur in the presence of tissue juice containing no organized cells. An oxidative, possibly phosphorylating, type of enzyme system appears to be involved. Muscle and prostate do not appear to metabolize testosterone significantly in this manner.

HYALINIZATION OF SEMINIFEROUS TUBULES AND CLUMPING OF LEYDIG CELLS: CHARACTERIZATION OF THE CLINICAL SYNDROME, ITS PHYSIOLOGY, DIAGNOSIS AND TREATMENT. *Heller, Carl G.* and *Warren O. Nelson.* Departments of Medicine and Anatomy, Wayne University College of Medicine, Detroit, Michigan.

A study of the clinical characteristics, hormonal excretion and testicular biopsies of twenty patients with hyalinization of the seminiferous tubules has led us to expand the limits of the syndrome recently described by Klinefelter, Reifenstein and Albright. In order to be admitted to the present category a patient must have the following: A) *Constant features* which are invariably present—1) small atrophic testes in which biopsy reveals hyalinization of the tubules and clumping of Leydig cells, 2) azoöspermia, 3) elevation of urinary gonadotrophins; B) On the basis of their *variable features* the patients are further classified as belonging to one of the following three subdivisions—1) eunuchoidal, 2) moderately eunuchoidal or 3) normal. These variable features include: a) skeleton which may or may not exhibit delay in osseous development and may show eunuchoidal or normal measurements; b) gynecomastia may be marked, mild or absent; c) external genitalia vary from completely infantile to entirely normal; d) the pattern of hair distribution may be prepuberal, puberal or normal adult in type; e) pitch of voice may be high or low; f) muscle development and strength vary from poor to normal; g) Leydig cells vary in quality; h) 17-ketosteroid excretion may vary from normal to very low; i) estrogens are not elevated, but may be normal or low. Physiology and therapy will be discussed.

HYALINIZATION OF SEMINIFEROUS TUBULES AND CLUMPING OF LEYDIG CELLS: MICROSCOPIC PICTURE IN THE TESTIS AND ASSOCIATED CHANGES IN THE BREAST. *Nelson, Warren O.* and *Carl G. Heller.* Departments of Anatomy and Medicine, Wayne University College of Medicine, Detroit, Michigan.

In the syndrome under consideration the testes are small (pea-size to almond-size). The seminiferous tubules are small and uniformly show hyalinization of the lamina propria. This is a progressive process and varies from a minor degree of sclerosis to complete hyalinization. Spermatogenesis is affected in proportion to the extent of the sclerotic process. In most testes Sertoli cells only are seen and in completely hyalinized tubules even these are absent. In all instances the interstitial cells of Leydig are clumped to a greater or lesser degree. These clumps frequently are so large as to suggest small adenomatous growths. The number and condition of the Leydig cells are variable and in agreement with the clinical picture and excretion of 17-ketosteroids. The more masculine patients have Leydig cells which are more numerous and which present a picture of activity, while the interstitial cells in less masculine patients usually are less numerous and present a picture of diminished function. The microscopic condition of the breasts varies from that usually encountered in normal males to one of hyperplasia of the parenchymatous elements and the interlobar stroma. The extent of the change corresponds in general with the presumed functional activity of the cells of Leydig.

SOME EFFECTS OF TESTOSTERONE, TESTOSTERONE PROPIONATE, METHYL TESTOSTERONE, STILBESTROL, AND X-RAY THERAPY IN A PATIENT WITH CUSHING'S

SYNDROME. *Martin L. Deakins, Harry B. Friedgood,* and *Joseph W. Ferrebee.* The Laboratory of Dental Medicine, Harvard School of Dental Medicine; the Department of Medicine, Harvard Medical School; and the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.

The metabolic and clinical effects of testosterone propionate, stilbestrol, methyl testosterone and testosterone were observed under controlled conditions in a girl, aged 15, with Cushing's syndrome. Injections of testosterone propionate, 25 mg. per day, caused a diminution in nitrogen excretion and a disappearance of creatinuria. Stilbestrol, 2 to 10 mg. per day, orally, did not affect nitrogen excretion but perhaps induced a moderate increase in creatine excretion and a decrease in creatinine excretion. Methyl testosterone, 40 mg. per day, orally, caused a striking decrease in nitrogen excretion and a tremendous increase in creatine excretion; creatinine excretion remained unaltered. Testosterone, 40 mg. per day, orally, did not produce unequivocal changes in excretion of nitrogen, creatine or creatinine.

Irregular increases in 17-ketosteroid excretion occurred during administration of testosterone propionate. Methyl testosterone caused an initial 3-day increase in 17-ketosteroids followed by a depression. Free testosterone caused a precipitous and marked rise in 17-ketosteroid excretion.

The androgens induced distressing accentuation of acne, hirsutism and hypertrophy of the clitoris. Stilbestrol improved these conditions but the benefit was not striking and was associated with certain toxic reactions and a transient hyperglycemia. X-ray therapy appeared to improve the subjective and objective manifestations of the disease.

CASE OF CUSHING'S SYNDROME TREATED WITH TESTOSTERONE PROPIONATE. *Whitelaw, M. J.* Charles S. Wilson Memorial Hospital, Johnson City, New York.

The case is presented of a boy, age 17, showing typical signs of Cushing's syndrome, osteoporosis of the spine and ribs, diabetic glucose tolerance curve, resistant to insulin, hypertension, decrease in libido, hirsutism, generalized muscular weakness and buffalo type of fat distribution and purple striae with normal genitalia. The 17-ketosteroids were normal. The serum sodium was markedly elevated. X-ray plates of the sella turcica and adrenal regions showed normal conditions. Under testosterone propionate treatment the boy showed marked gain in strength.

TITERS OF URINARY GONADOTROPINS IN OLD EUNUCHS WHO HAD BEEN CASTRATED PREPUBERTALLY AND EVIDENCE OF SUPRANORMAL SECRETORY ACTIVITY OF AN ENDOCRINE GLAND FOR FORTY TO FIFTY YEARS. *Hamilton, James B., Hubert E. Catchpole,* and *Charles C. Hawke.* Departments of Anatomy Yale University and University of Missouri Schools of Medicine, and the Adolescence Study Unit and Laboratory of Physiology, Yale University School of Medicine, New Haven, Connecticut.

Four men, who had been castrated between eight and twelve years of age and at the time of the present study had been eunuchs for 44 to 51 years, excreted large quantities of urinary gonadotropins—160, 160, 40 and between 40 and 80 M.U. daily. These values far exceeded the average daily excretion of 10–25 M.U. by ten normal men 55 to 76 years old. The presence of large amounts of urinary gonadotropins in prepubertally-castrated eunuchs seems to date from the normal chronological age of puberty, if not slightly earlier, as judged by collateral studies of two boys castrated before the advent of manifest puberty. If elevated titers of gonadotropins in castrate individuals reflect augmented secretion of gonadotropins by the pituitary gland, the continued production of greatly supranormal quantities of gonadotropins during most of the lifespan of these eunuchs provides a striking illustration of prolonged hyperfunction of an endocrine gland. Although primary gonadal insufficiency comparable to that in women past the menopause does occur

in old men, as after bilateral orchidectomy or destruction of the testes, climacteric-like conditions would not appear to be either a usual or a normal sequela of ageing in men.

THE USE OF THE SOMATOTROPIC PROPERTIES OF TESTOSTERONE PREPARATIONS IN CHRONIC DEBILITY.* *Reifenstein, Edward C., Jr., Anne P. Forbes, Lawrence W. Kinsell,* and *Fuller Albright.* From the Department of Medicine of the Harvard Medical School and from the Medical Service of the Massachusetts General Hospital, Boston, Massachusetts.

Testosterone compounds induce retention of nitrogen, sulfur, potassium, and phosphorus in the proportions that they exist in protoplasm. The evidence indicates that these substances possess protoplasmic anabolic (somatotropic) properties. Loss of protoplasm accompanies many disease processes: in most instances at the proper time during convalescence anabolism of protoplasm occurs spontaneously and restores the integrity of the tissues. Evidence suggests that these adaptations of the individual to a damaging event are under the control of the adrenal cortex; these phenomena have been discussed by Selye under "the alarm reaction." In chronic debility the phase of protoplasmic anabolism fails to occur; hence treatment with somatotropic agents seems indicated. The present investigations consist of nitrogen balances and other pertinent data before and after testosterone therapy in a patient with chronic debility (rheumatoid arthritis) and in a patient on an inadequate protein diet. In the former tissue anabolism was initiated; in the latter tissue catabolism for energy purposes was inhibited.

THE EFFECTS OF TESTOSTERONE, TESTOSTERONE PROPIONATE, AND PREGNENOLONE ON PROTEIN FABRICATION IN MAN. *Abels, Jules C., Nelson F. Young, Howard C. Taylor, Jr., C. P. Rhoads.* Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York City.

Ninety mg. of testosterone or 100 mg. of testosterone propionate were administered daily to 5 male subjects for from 7 to 40 days. The subjects were maintained on constant diets of known nitrogen content. The steroids administered induced nitrogen retention to account for from 200 to 392 gm. of protein. However, the total circulating albumin and globulin decreased in all instances. With further administration of the steroids, the circulating protein fractions eventually increased towards the pretherapy level. The plasma volume and extra cellular fluid were not significantly effected by either testosterone or its propionate. One hundred mg. of pregnenolone were later administered daily to one subject for 36 days. Although this steroid induced considerably less nitrogen retention than did the testosterone, the amount of circulating protein formed was considerably greater. No preliminary decrease of circulating protein occurred. The simultaneous increase in extracellular fluid and plasma volume was so great that the subject became edematous. It would appear from these studies, therefore, that the administration of testosterone or testosterone propionate primarily induced tissue protein fabrication even at the expense of circulating protein. In contrast, pregnenolone induced primarily circulating protein formation, but the associated extra-cellular water retention was too great to suggest clinical use for this material.

COMPARISON OF URINARY 17-KETOSTEROIDS OF TESTICULAR AND ADRENAL ORIGIN. *McCullagh, E. Perry* and *Wendell Bowman.* Cleveland Clinic, Cleveland, Ohio.

Colorimetric determinations for 17-ketosteroid and androgen bio-assays were done on a group of five male castrates and six male patients with Addison's disease

* These studies were supported by grants from the Josiah Macy, Jr. Foundation; and from the Committee on Endocrinology of the National Research Council. The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts General Hospital.

The results were compared to determine what difference, if any, existed between the two groups. Steroids in the castrate should come from the adrenals, while those in the Addison's patient should be derived principally, if not wholly, from the gonads. Forty-eight hour specimens of urine were pooled, hydrolyzed, and extracted with butyl ether. One half of the butyl ether extract was assayed for androgens by the capon comb growth method. The other half was fractionated into ketonic, non-ketonic, and total neutral fractions. The average androgen level in the castrate group was 6.9 I.U., and in the Addison's group was 8.4 I.U. For the ketonic fractions 17-ketosteroids were 3.3 and 3.5 mg. per 24 hours respectively. The castrate group showed some correlation between the ketonic fractions and the androgen assays. The Addison's group did not. No measurable β-ketosteroids could be found in the pooled extracts of either group. As anticipated, similar determinations in women with Addison's disease showed a very low level of 17-ketosteroid excretion even in the total neutral fraction. Fractionation showed that practically all the color was due to nonketonic chromogens. It seems evident that the similarity of the assays in the castrate and Addison's groups makes it impossible to show any difference as judged by the data observed. However, since the majority in both groups were in fairly good health it seems reasonable that the sum of the average 17-ketosteroid values for the ketonic fractions of both groups could be taken as the lower limit of the normal 24-hour range. This would bring the values for the total crude extract to about 11 mg. and those for the ketonic fraction to about 7 mg. per 24 hours. Further observations regarding quantitative gonadotropins, sperm counts, and prostatic atrophy have been made in these cases.

METABOLIC STUDIES ON THE URINARY EXCRETION OF KETOSTEROIDS IN NORMAL INDIVIDUALS AND IN PATIENTS WITH ADRENAL DYSFUNCTION AND CANCER. *Dobriner, Konrad, C. P. Rhoads, Seymour Lieberman, B. R. Hill, Louis F. Fieser.* Memorial Hospital, New York City, and Converse Memorial Lab. Harvard University, Cambridge, Massachusetts.

The determination of the 17-ketosteroid levels in the urines of normal individuals and of patients does not allow for a distinction between the different kinds of steroids excreted nor does it permit the quantitative estimation of the amount of each compound present, both of which may be significant for certain disorders. Individual urine collections were made and the steroid content studied in a group of normal men and women of different ages, in pregnancy, in patients with adrenal dysfunction (adrenal hyperplasia, cortical tumor and Cushing's syndrome), and in patients with cancer and with leukemia. The neutral fractions obtained from these urines were separated into the ketonic and non-ketonic material. The ketonic components were further divided into their alpha and beta ketonic fractions. The non-ketonic material was separated into its alcoholic and nonalcoholic constituents. A total of 33 different ketosteroids were isolated by systematic quantitative chromatographic analysis of the alpha ketosteroids from individual urines. Seven of these have been previously described in the literature. Only 9 alpha ketosteroids are constantly found in the urine of normal men and women. Their distribution also also follows a consistent pattern. About 60 to 70 per cent of the alpha ketosteroid fraction consists of androsterone and its isomer, alpha hydroxyaetiocholanolone which were present in a ratio of about 1:1. The urine of pregnant women and of patients with adrenal hyperplasia and adrenal cortical tumors revealed not only the presence of a great number of ketosteroids not found in normal urine, but also a distinct difference in the pattern of their distribution. In the urines of the there cancer patients studied completely, ketosteroids were present which were not found in the urine of six normal persons. In others, androsterone was absent or an abnormal ratio of androsterone to aetiocholanolone was found; this ratio is similar to that in adrenal hyperplasia or pregnancy. The study of the alpha ketosteroid

patterns in normal and diseased individuals revealed marked differences in the distribution and types of compounds present. These results give more detailed information with regard to the disturbances of steroid metabolism.

THE URINARY 17-KETOSTEROIDS OF A PATIENT WITH AN INTERSTITIAL CELL TUMOR OF THE TESTES. *Hoffman, M. M.* McGill University Clinic, Royal Victoria Gospital, Montreal, Canada.

The urine of a man, 41 years of age, with a malignant tumor of the interstitial cells of the testis with extensive metastases was adjusted to pH 1 and extracted with butanol. The extract was submitted to simultaneous hydrolysis and extraction. The neutral fraction of the hydrolyzed material was separated into ketonic and non-ketonic substances. The ketonic substances were further fractioned into digitonin-precipitable and digitonin-non precipitable hydroxy-ketones and non-hydroxy-ketones. Each of these three fractions was submitted to repeated chromatographic analyses. Isolated and identified, with yields expresssed as milligrams per 24 hours, were androsterone (271.6) aetiocholanol-3 (α)-one-17 (62), Isoandrosterone (6.1), and Δ^2-androstenone-17 (38.1). Dehydroisoandrosterone could not be isolated. In addition to these, a number of unidentiqed compounds have been isolated. Androsterone accounts for most of the urinary 17-ketosteroids excreted by this patient, whereas in patients with carcinoma of the adrenal cortex dehydroisoandrosterone appears to be the major urinary 17-ketosteroid. The failure to isolate dehydroisoandrosterone in this case supports the hypothesis that this steroid is a metabolite of the steroid hormones of the adrenal cortex rather than of the testicle.

THE EXCRETION OF NEUTRAL URINARY STEROIDS IN STRESS. *Freeman, William. Gregory Pincus,* and *Everett D. Glover.* Research Service of the Worcester State Hospital and the Physiological Laboratories, Clark University, Worcester, Massachusetts.

Normal male subjects and mental patients have been subjected to the stresses of exposure to cold, pursuit-meter operation and psychological tests. The excretion of 17-ketosteroid during control and stress periods has been determined by the application of the Zimmerman and $SbCl_3$ reactions to the neutral ketonic fractions of urines collected during these periods. The normal subjects regularly exhibit an increased excretion of 17-ketosteroid during stress with a sharp post-stress decline. Responses among the patients are varied, but failure to show the stress rise is rather general, and a rise in 17-ketosteroid excretion in the post-stress period is marked. The excretion of atypical neutral steroid by the patients and of quantitatively abnormal β-ketosteroid is indicated.

THE EFFECT IN MAN OF CHRONIC INTERMITTENT ANOXIA ON GLUCOSE TOLERANCE AND THE URINARY EXCRETION OF SODIUM, POTASSIUM, CHLORIDE, PHOSPHORUS, NITROGEN AND 17-KETOSTEROIDS.* *Bryan, A. Hughes* and *Henry I. Ricketts.* Department of Medicine, School of Medicine, University of Chicago, Chicago, Illinois.

A considerable body of evidence has shown that exposure of anoxia profoundly affects the adrenal cortex of animals. The rapid development of aviation has made it desirable to determine whether anoxia produces in man the evidence of adrenal cortical stimulation observed in animals. To this end, 5 experiments were performed on 4 human subjects, 19 to 28 years of age, exposed without much physical activity to altitude pressures of 11,500, 16,600, and 18,000 feet from 4 to 6 hours

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago.

daily, 6 days a week, for from 4 to 6 weeks. The subjects were on constant weighed diets and careful metabolic technic was followed throughout. The observations consisted of (1) measurements, in fractional and 24-hour urine specimens of sodium, potassium, chloride, phosphorus, nitrogen and 17-ketosteroids and (2) glucose tolerance. In some cases complete balance studies were done. With the possible exceptions of a slight increase in potassium excretion in two subjects a transient rise in 17-ketosteroid excretion in one subject and a moderate decrease in tolerance for glucose in two, the results obtained provide no evidence that the human adrenal cortex is influenced by chronic intermittent anoxia under the conditions of these experiments.

THE 17-KETOSTEROID EXCRETION IN DAMAGE AND CONVALESCENCE. *Stevenson, J. A. F., Victor Schenker,* and *J. S. L. Browne.* McGill University Clinic, Royal Victoria Hospital, and the Henry J. Elliott Research Laboratory, Shriner's Hospital, Montreal, Canada.

The daily excretion of total neutral 17-ketosteroids in the urine has been studied, using the Holtorf-Koch modification of the Zimmerman reaction, in some 30 males following various types of damage, (burn, fracture, operation, infection, hemorrhage) during convalescence, and in four healthy males. The majority were previously healthy, suffering acute damage, but some were chronically ill patients undergoing operation. In those followed from the onset of damage a sharp rise in 17-ketosteroid output (confirming Forbes) followed by an immediate fall was frequently but not invariably observed. There was then a gradual rise in daily excretion as convalescence progressed. During convalescence, marked peaks of 17-ketosteroid excretion were frequently seen, not only on further damage such as minor operations, infections, etc., but also on exertion, such as, first time in wheel chair, first walk, etc., which were not associated with changes in 17-ketosteroid in the later convalescence or in healthy active people. In two male children followed during damage, the 17-ketosteroid exretion remained relatively constant. The significance of these changes in 17-ketosteroid excretions and their possible relationship to adrenocortical function in damage, the differences in reaction of the healthy, the chronically ill, the child, and the convalescent are discussed.

PROBLEMS IN THE TREATMENT OF CARDIAC FAILURE IN MYXEDEMA. *McGavack, T. H.,* and *David Schwimmer.* New York Medical College, New York City.

The major problem confronting the clinician who must treat myxedema complicated by cardiac failure is the necessity for restoring the competency of the heart while increasing the load it must assume. Patients with hypothyroidism with demonstrable cardiac disease have been studied in states of thyroid insufficiency and cardiac failure. The influence of desiccated thyroid substance on cardiac compensation and thyroid insufficiency have been correlated with values for the basal metabolic rate, the circulation time, cholesterol and cholesterol esters of the blood, and capillary permeability. From these data, effort will be made to establish criteria by which therapy may be applied satisfactorily.

THE INFLUENCE OF THYROIDECTOMY ON THE PROMINENCE OF THE EYES IN THE GUINEA-PIG AND IN MAN. *Dobyns, B. M.* The Mayo Foundation, Rochester, Minnesota.

A new and more accurate method of measuring exophthalmos in guinea-pigs has been devised. This method was employed to determine the day-by-day changes in the prominence of the eyes of guinea-pigs after thyroidectomy. The experiment was controlled by a new application of skull measurement and by control experiments on normal animals. An increase in the prominence of the eyes after thyroidectomy was found. Histologic changes were studied in various tissues. Exophthalmometric measurements were obtained in 233 consecutive cases of

exophthalmic goiter and adenomatous goiter with or without hyperthyroidism. Measurements were made before and at intervals of one to four days after thyroidectomy. In all but nine cases some increase in the prominence of the eyes developed after thyroidectomy. This increase appeared to bear some relation to the basal metabolic rate. Less or no significance was found in its relation to the size of the thyroid, the amount of thyroid removed, the previous prominence of the eyes, the presence of thyroiditis and the sex. Control observations were made on patients subjected to other surgical procedures.

NON-PERMEABILITY OF THE MAMMARY GLAND TO SYNTHETIC THYROPROTEIN. *Turner, C. W.* and *E. P. Reineke.* University of Missouri, Columbia, Missouri.

Guinea pigs were given approximately 100 ml. of milk daily for two weeks from cows receiving massive doses of protamone (synthetic thyroprotein). In a second trial with guinea pigs, milk from cows receiving a moderate dose of protamone was fed for six weeks. Frequent determinations of metabolism during both experiments failed to show any significant differences between these animals and paired controls receiving a normal milk diet, or normal guinea pigs on a stock diet. The experimental group while still on the milk diet showed a 25 per cent increase in metabolism when 2.5 mcg. of 1-thyroxine was injected daily for two weeks. In a similar experiment with thyroidectomized goats no metabolic stimulation or observable improvement of the cretinism could be detected as a result of feeding milk from protamone-fed cows for two weeks. These animals responded markedly, however, when $\frac{1}{4}$ gram of protamone daily was fed directly. No elevation of the basal metabolism could be detected when a quart of milk daily from protamone-fed cows was consumed by two human subjects. Significant elevation of the basal metabolic rate occurred when $\frac{1}{4}$ to 1 grain of protamone daily was given orally. It was concluded that the mammary gland does not permit passage of biologically detectable amounts of thyroidal hormone when protamone is fed to lactating cows.

IMMUNE REACTIONS IN RABBITS AND RATS AFTER INJECTIONS OF THYROID GLOBULIN. *Meyer, Arthur E., Constance M. Stickney, David Marine* and *Jacob Lerman.* From the Research Laboratories, The Maltine Company, the Laboratories Division, Montefiore Hospital, New York and the Thyroid Clinic of the Massachusetts General Hospital, Boston, Massachusetts.

Sterile solutions of globulin from human and pig thyroids were injected intraperitoneally in rabbits at suitable intervals. An initial rapid loss in weight was followed by slow gain. The increased metabolism, however, persisted on continued treatment for 10 weeks. The precipitin test in the serum became positive at a dilution of 1:10,000. The thyroids of the treated rabbits were small but produced metabolic stimulation when fed to thyroidectomized rats. The testes showed decreased spermatogenesis. Injection of the anti-thyroid serum into normal rabbits caused a drop in B.M.R. and prevented the response to injected thyroid globulin. Prolonged injections in rats inhibited the thyroids but produced no detectable antibodies. Sera from such rats did not prevent the full effect of thyroid globulin when injected into other rats. Spermatogenesis was not affected in the rat.

ON THE MECHANISM OF ALLOXAN DIABETES. *Goldner, Martin G.* and *George Gomori.* Department of Medicine, University of Chicago.

It has been shown in previous experiments by ourselves and others that a single intravenous injection of alloxan produces sustained diabetes mellitus in dogs, rats and rabbits. The anatomical basis of this diabetes is the degeneration of the islets of Langerhans, especially of the beta cells. The mechanism of alloxan diabetes has been further investigated. Alloxan-treated animals show glucose tolerance tests typical of diabetes mellitus; the diabetes improves on carbohydrate restriction

and on insulin treatment. Alloxan does not inhibit the action of insulin. Simultaneous treatment with insulin and alloxan prevents the development of hyperglycemia but does not protect against the necrosis of the islet cells. Pre-treatment with phloridzin does not prevent the development of alloxan diabetes. Adrenalectomy prevents the initial alloxan hyperglycemia, and the transitory alloxan hypoglycemia does not occur after pancreatectomy. Assays have proved that the pancreas of alloxan diabetic dogs is depleted of insulin. Several chemical compounds related to alloxan (e.g., alloxantin, dialuric acid, violuric acid and barbituric acid) were found ineffective. Alloxan in a buffered solution was also ineffective.

MODIFIED PROTAMINE ZINC INSULIN: COMPARISON WITH GLOBIN ZINC INSULIN AND WITH EXTEMPORANEOUS MIXTURES. *MacBryde, Cyril M.* and *Robert S. Reiss.* Department of Internal Medicine, Washington University School of Medicine, and the Barnes Hospital, St. Louis, Missouri.

In more than 100 diabetic patients modified protamine zinc insulin controlled the majority of uncomplicated cases with a single injection daily. Three-fourths of the insulin content acts slowly, while one-fourth acts rapidly. Of numerous extemporaneous mixtures, the one containing two parts crystalline to one part protamine zinc insulin seems most promising. Modified protamine zinc insulin was compared directly with globin zinc insulin and with the 2:1 mixture in a series of carefully controlled diabetic patients. Twenty-four hour blood sugar curves were obtained. It appeared that any of the intermediate insulins, as well as standard protamine zinc insulin, give fairly good results when the single dose is less than 40 units daily. Differences between the insulins become apparent with larger doses. Globin zinc insulin causes mid-afternoon hypoglycemia frequently. It also fails to control the rise in blood sugar after breakfast. The 2:1 mixture gives irregular results, with a tendency toward early morning hypoglycemia. The rise in the blood sugar after breakfast is partly controlled, but less well than with modified protamine zinc insulin. Modified protamine zinc insulin establishes better regulation than globin zinc insulin or the 2:1 mixture or other mixtures tried. With a single dose before breakfast the blood sugar can be kept within approximately normal limits during the night as well as during the day.

REVIEW OF 100 CASES OF DIABETIC NEUROPATHY FOLLOWED FROM ONE TO TEN YEARS.* *Rudy, Abraham* and *Samuel H. Epstein.* Medical and Neurologic Services of the Beth Israel Hospital, Boston, Massachusetts.

Diabetic neuropathy is a disseminated neurologic disturbance involving the entire nervous system, central as well as the peripheral. Only half the cases reviewed showed signs of peripheral neuropathy. It was most common between the ages of 50 and 70 years; least common below 40. Loss of weight preceded the neurologic symptoms in over half of the cases. The neuropathy occurred in acute diabetes before treatment was instituted and in some cases soon after control by diet alone or with insulin. It was observed in all types of diabetes mild and severe, controlled, semicontrolled and uncontrolled. Half of the cases were on a diet with insulin, when the neuropathy developed. In only 66 cases the diet was inadequate. Diabetic neuropathy is frequently accompanied by generalized manifestations of thiamine deficiency. In 41 cases signs of deficiency in various B vitamins were seen. In 90 per cent of the cases no vitamin therapy had been used before the neuropathy developed while 93 per cent received vitamin B in some form during the treatment of the neuropathy; 27 cases received yeast only and 45 cases were given parenteral thiamine chloride and some vitamin B-complex also. Marked improvement of the

* Aided by a grant from the Charlton Research Fund, Tufts College Medical School.

neuropathy was seen in 74 cases. Only 37 cases recovered in less than 6 months and 29 cases in about 6 to 12 months. Several were completely cured of subjective complaints and abnormal neurologic manifestations.

PLASMA PROTEIN STUDIES IN DIABETES MELLITUS BY TISELIUS ELECTROPHORESIS TECHNIC. *Lewis, Lena A., Robert W. Schneider,* and *E. Perry McCullagh.* From the Departments of Physiology and Endocrinology, Cleveland Clinic Foundation, Cleveland, Ohio.

Plasma proteins in diabetes mellitus have been extensively studied in the past, using chemical precipitation for estimating the albumin-globulin content. In hopes that further information might be obtained on changes in plasma-protein fractions in various stages of the disease, electrophoretic studies were undertaken by Longworth's method with phosphate buffer pH 7.8. Total nitrogen was determined by Pregl's modification of the micro-Kjeldahl method. In uncomplicated diabetes showing extreme acidosis, total protein was normal but albumin greatly decreased. Most of the increase in globulin occurred in the β-fraction; α- and γ-globulin and fibrinogen remained normal. After diabetic control and months of adequate nutrition the protein picture was entirely normal. In a case of diabetic acidosis complicated by Staphylococcus aureus infection a marked increase in α- and β-globulin occurred. In many infections a high α-globulin with no increase in β-globulin is observed. In mild uncomplicated diabetes with very slight or no acidosis, the total protein was low but the relative percentage of albumin, α-, β-, and γ-globulin and fibrinogen was normal. After control of the diabetes the protein level rose to normal. Studies on diabetics showing retinal changes when the diabetes *per se* was well controlled showed low albumin and decreased or low normal total protein. Preliminary studies following a very high protein diet indicated some increase in albumin.

A STRESS-SURVIVAL TEST FOR CORTIN.* *Elmadjian, Fred* and *Gregory Pincus.* From the Physiological Laboratories, Clark University, Worcester, Massachusetts.

Adrenalectomized 40 to 60 gram rats tied down to a wire grid by all four legs for one hour exhibit symptoms of shock and die within four hours. The administration of desoxycorticosterone acetate, adrenal cortex extract, and certain 11-oxygenated corticosteroids prolongs survival. Typical dosage-response curves may be obtained with a variety of corticoid substances. The usefulness of this method as a quantitative assay for cortin will be discussed.

CORTIN-LIKE MATERIAL IN HUMAN AND MONKEY URINE. *Dorfman, Ralph I., Reginald A. Shipley, Benjamin M. Horwitt,* and *William E. Abbott.* Brush Foundation and Departments of Biochemistry, Medicine and Surgery, Western Reserve University, School of Medicine and Lakeside Hospital, Cleveland, Ohio.

Cortin-like material previously demonstrated in normal men's urine has been shown to be present also in the urine of normal women and of monkeys. Evidence is presented which indicates that this material arises in the adrenal gland and that the urinary concentration of cortin-like material may well be an index of adrenal cortical activity. Urinary cortin-like material was assayed by means of a cold protection test using immature adrenalectomized rats. Significance of difference between mean survival time of extract-treated and control rats was calculated. Urinary cortin-like material has been studied in intact, gonadectomized, adrenalectomized and gonadectomized-adrenalectomized monkeys—nine in all. Cortin-like material was found in 11 of the 21 urines from intact monkeys and in 4 of 9 urines from gonadectomized monkeys. This material was not found in any of 6 urines

* Aided by a grant from G. D. Searle and Company.

collected after adrenalectomy. In 6 experiments the administration of adrenal cortical extracts to adrenalectomized monkeys invariably was followed by the reappearance of cortin-like material in the urine. In 1 of 3 experiments, urinary cortin-like material was demonstrable after the administration of desoxycorticosterone to adrenalectomized monkeys. Urinary cortin-like material was studied in 9 normal men, 8 normal women and in 7 patients with Addison's disease. The urines of all men and women studied contained cortin-like material while only once in 15 assays of Addison's-disease urine was it possible to demonstrate active material. In 3 of 5 experiments in which adrenal cortical extracts were administered to Addison's-disease patients, significant amounts of active material were found in the urine. Studies on ethylene dichloride or chloroform extracts of normal men's urine disclosed that the active material is in the ketonic neutral fraction. At least a portion of the active material in urine appears to be present in a combined form.

CORTIN-LIKE SUBSTANCES IN URINE. *Venning, Eleanor H., M. M. Hoffman,* and *J. S. L. Browne.* McGill University Clinic, Royal Victoria Hospital, Montreal, Canada.

A method, based on solvent partition, is described for the extraction and purification of cortin-like substances in urine. This method permits a 25- to 100-fold concentration of the biologically active substances with a loss of approximately 25 per cent of the activity present in the crude urinary extracts. Extracts from postoperative urine are capable of maintaining the adrenalectomized rat, of protecting it against the lethal action of cold, and of causing glycogen deposition in the liver of the fasted adrenalectomized rats. Urine excreted after operation was found to contain three to 30 times the amount of cortin-like substances excreted by normal men. The active substances are ketones. Highly purified ketonic fractions contain 25 to 100 cold units per milligram (one cold unit represents the activity of ten gamma of corticosterone in the modified Selye-Schenker cold exposure test). The mouse has been used as a test animal for assaying the liver glycogen deposition effect of individual 24- or 48-hour specimens of urine. The excretion of these substances has been followed in normal males and females following muscular exercise and damage.

STUDY OF THE "ALARM REACTION" IN BURNED HUMAN SUBJECTS AND ITS POSSIBLE SIGNIFICANCE IN WAR INJURIES.* *Glendening, Mary Beth, Helen A. Winter, H. H. Williams, W. E. Abbott, J. W. Hirshfeld,* and *Carl G. Heller.* Departments of Medicine and Surgery, Wayne University College of Medicine, the Medical and Surgical Services of the City of Detroit Receiving Hospital and the Research Laboratories of the Children's Fund of Michigan.

This study is designed to correlate changes in nitrogen balance in burned patients with change in endocrine function which might accompany the "alarm reaction" in human beings. The excretion of estrogens, gonadotrophins, 17-ketosteroids, cortins and nitrogen intake and output have been followed for 1 to 7 five-day metabolic periods, beginning immediately after the burn was sustained. Estrogenic excretion tended to be higher during the first 10 days than subsequently, but remained within the limits of normal variation except that an abnormally high level was encountered in the most severely burned male patient. The excretion of gonadotrophic hormone remained within normal limits during the first 20 days following the burn. Subsequently increases were noted. In some cases the levels returned to normal. However, in one patient the increased levels of excretion were still observed one month after recovery. The 17-ketosteroid excretion fluctuated

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Wayne University College of Medicine.

within the range of normal values. The concomitant occurrence of negative nitrogen balance and elevation of cortin excretion taken together with the changes in excretion of other hormones may elucidate the physiology involved in nitrogen retention and the repair of tissue and may suggest therapy for burned and wounded servicemen.

THE ROLE OF THE ADRENALS AND HYPOPHYSIS IN THE CONTROL OF SYSTOLIC BLOOD PRESSURE IN THE RAT. *Leathem, J. H.* and *V. A. Drill.* Department of Zoology, Rutgers University, New Brunswick, and the Department of Biology, Princeton University, Princeton, New Jersey.

Systolic blood pressure of the rat was studied in unanesthetized adult males following adrenalectomy, hypophysectomy and after administration of adrenal hormones. Normal blood pressures ranged between 110 and 120 mm. Hg. Adrenalectomy caused a sharp decrease in blood pressure which averaged 60 mm. six days postoperatively. A slight rise may occur followed by a fall in pressure below 60 mm. and death of the animal. Hypophysectomy is followed by a decrease in pressure to 80 mm. However this subnormal pressure is maintained for as long as seven months. A daily dosage of desoxycorticosterone acetate (0.5 mg.) that will maintain blood pressure at essentially normal levels in adrenalectomized rats for 20 days failed to prevent the drop in pressure following hypophysectomy. This dosage of D.C.A. seldom caused a mild hypertension in normal rats. Large doses of adrenal cortical extract, however, partially prevented the decrease in blood pressure following hypophysectomy. Average pressure 15 days postoperatively in treated rats was 95 mm. as compared with 83 mm. for operated controls and 111 mm. for the normal rat. It would appear that some factor in addition to the loss of cortical hormone is responsible for the lowering of systolic blood pressure after hypophysectomy in rats.

ESTROGEN FROM THE ADRENAL GLANDS. *Schiller, Joseph.* The Physiological Laboratory, Boston University, Boston and the Physiological Laboratories, Clark University, Worcester, Massachusetts.

Two mgm. per day of a highly purified adrenocorticotropic hormone preparation were administered by injection twice daily to several groups of adult female rats (7–10 animals per group). Daily variations in the vaginal smear were observed. No change was observed in normal diestrus females, but animals injected during estrus exhibited prolonged cornification. Ovariectomized and ovariectomized-adrenalectomized rats exhibited no vaginal smear changes. Proestrus smears were induced in ovariectomized partially hepatectomized rats. The proestrus smears resulting from partial hepatectomy in normal females were converted to fully cornified smears. Production of estrogen from the adernal cortex by corticotrophin stimulation is indicated. The adrenal glands of 8 mature female rats were grafted into the spleen. The estrous cycle was unaffected. All tests of adrenal cortex function such as life maintenance, cold resistance, liver glycogen and blood sugar levels indicated normality.

Papers Read by Title

THE INFLUENCE OF ADMINISTERED HORMONES IN PITUITARY INFANTALISM: CASE REPORT. *McGavack, T. H.* and *Kurt Lange.* New York Medical College, New York City.

A 49-year-old male with infantilism due to craniopharyngioma was studied. The influence of testosterone propionate, desoxycorticosterone acetate, α-estradiol dipropionate, and several pituitary extracts upon his generally depressed metabolic status was studied in relation to his general sense of well being and various laboratory findings. These included blood chemical findings (cholesterol and esters,

intravenous glucose-tolerance tests, and sodium and potassium); urinary excretion of creatine, sodium, potassium, and chloride; inulin clearance; capillary permeability; and response to ingestion of water as determined by the Kepler-Robinson test.

TREATMENT OF PITUITARY DWARFISM WITH CHORIONIC GONADOTROPIN AND MALE SEX HORMONE: END RESULTS. *Thompson, Willard O., Norris J. Heckel,* and *Phebe K. Thompson,* University of Chicago, Chicago, Illinois.

We have previously shown that in young boys chorionic gonadotropin and male sex hormone will cause rapid acceleration of growth similar to that which occurs normally at the time of puberty without treatment. The effect of these materials has now been observed in pituitary dwarfs over a period of several years. In this condition they also cause rapid growth, which involves not only the skeleton but also every tissue of the body, particularly the musculature. In the course of from 2 to 5 years the rate of growth decreases as epiphyseal closure sets in. The maximum increase in height observed was about 8 inches. The amount of growth appeared to be greater when treatment was started at the age of 9 to 10 years than when it was started at the age of 15 to 16 years. When the dwarfism was marked it was impossible to cause the skeleton to achieve normal height with these materials. The following conclusions would appear to be warranted. Male sex hormone will cause rapid acceleration of growth in pituitary dwarfs before the age of epiphyseal closure. This acceleration of growth takes place in the absence of the pituitary growth factor and is probably the result of a direct influence of male sex hormone on the growth of bone and other tissues. Male sex hormone is not a substitute for the pituitary growth factor or thyroid hormone in stimulating growth. It appears to influence primarily the component of growth which takes place at the time of puberty, namely, skeletal moulding. The administration of chorionic gonadotropin or male sex hormone is desirable in pituitary dwarfism. Treatment should be started at the age of 10 to 12 years and continued until epiphyseal closure sets in. Only in this manner is it possible to insure that the growth associated with puberty will take place.

THE IN VITRO METABOLISM OF TESTOSTERONE BY RABBIT LIVER. *Clark, L. C., Jr.* and *C. D. Kochakian.* Department of Vital Economics, University of Rochester, Rochester, New York.

Rabbit liver slices were incubated with a suspension of testosterone in serum. The resultant mixture was analyzed by extracting with fat solvents and fractionating by chemical and physical means. The hydroxyketonic fraction yielded unchanged testosterone and very small amounts of cis-testosterone and a digitonin precipitable compound. The non-hydroxy-ketonic fraction consisted mainly of Δ^4-androstenedione-3,17. The non-ketonic fraction yielded a small amount of an unidentified 17-hydroxy compound. Some evidence was obtained for the existence of a conjugated testosterone.

THE INFLUENCE OF TESTOSTERONE PROPIONATE, METHYL TESTOSTERONE AND METHYL ANDROSTANEDIOL ON CREATINE METABOLISM. *Keutmann E. Henry, Samuel H. Bassett* and *Charles D. Kochakian,* Rochester, New York.

One eunuchoid, one undernourished and two normal young men were studied. Each had a constant small creatinuria probably caused by a constant amount of meat in the same daily diet.

Testosterone propionate caused a decrease of creatinuria. After withdrawal there was a rebound with a peak value about three times the amount in the control periods. Both the retention and the rebound were greater in the eunuchoid than normal persons. The excess creatine excreted during the rebound was more than the excess retained. This suggests that testosterone propionate accelerated the synthesis of creatine. Increased creatinine excretion supports this also.

Methyl testosterone and methyl androstanediol caused a decrease of creatinuria for a few days followed by a gradual increase to levels far above the control periods. With methyl androstanediol this continued for some time after withdrawal then decreased. When methyl testosterone was withdrawn there was a marked rebound from release of creatine which had previously been stored. Steady increase of creatinine excretion was observed while both compounds were given. This must mean that increased creatine was deposited.

A Study of the Intermediary Metabolism of Certain Adrenal Steroids.* *Pearlman, W. H.* and *Gregory Pincus.* Physiological Laboratories, Clark University, Worcester, Massachusetts.

Considerable indirect evidence supports the theory that the urinary 17-ketosteroids are in part derived from the adrenals but direct evidence is lacking to show that the numerous C-21 steroids elaborated by the adrenals are transformed in the animal body to 17-ketosteroids. The guinea pig is a suitable test animal for the study of 17-ketosteroid excretion following the administration of representative C-21 adrenal steroids for the following reasons: 1. Its small size allows the use of small amounts of the precious test compounds. 2. The guinea pig has been shown (Dorfman et al.) to be capable of excreting 17-ketosteroids following testosterone administration and to serve as a satisfactory subject for steroid metabolism studies. The 17-ketosteroid determinations were made on the neutral ketonic fraction of the urine extracts with the aid of the Zimmerman color test and also the antimony trichloride test of Pincus; the latter test appears to be more specific for 17-ketosteroids, especially for those closely related to androsterone. Current evidence indicates that typical urinary 17-ketosteroids may be derived from certain C-21 adrenal steroids.

Estimation of the Non-Ketonic Alcoholic Steroids in the Urine of Normal and Diseased Individuals. *Lieberman, Seymour* and *Louis F. Fieser.* Converse Memorial Lab. Harvard University, Cambridge, Massachusetts. *Konrad Dobriner,* and *C. P. Rhoads,* Memorial Hospital, New York City.

The application of the Zimmerman reaction for the quantitative determination of the 17-ketosteroids in the urine of normal and diseased individuals has yielded valuable clinical information. There has been no clinical method available for the quantitative estimation of the total non-ketonic alcoholic steroids. However, various investigators have demonstrated the presence of such compounds—especially pregnandiol. A method has been developed for the separation and quantitative estimation of the urinary non-ketonic alcoholic steroids. The method has been based on the formation of the phthalic or succinic half-esters of the alcohols and the subsequent electrometric titration of the resulting half-esters. The amounts of alcohol reacting are directly related to the acidity. The alcoholic steroids may be regenerated by the use of mild hydrolysis from the half-esters and the amount of steroid determined by weight or titration. The application of this technique to pure alcoholic steroids has resulted in the recovery of 90 to 100 per cent of the original material by the titration method and 95 to 105 per cent by the weight method. The application of these methods to the non-ketonic fractions obtained from human urines has given the following results. Normal men and women excrete 3 to 12 mg. per 24 hours. This increases to 30 to 50 mg. in cases of adrenal hyperplasia. In cases of tumors of the adrenal cortex, values of 27 to 83 mg. were obtained. In pregnancy the values were 24 to 27 mg. After the injection of 100 mg. of testosterone, only a slight increase of the non-ketonic alcohols was observed which is in contrast to the definite increase of the 17-ketosteroids. The main portion

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of the administered testosterone which does not appear as a ketonic metabolite also does not appear in the non-ketonic alcoholic fraction.

A Comparison of the Renotrophic with the Androgenic Properties of Steroids. *Kochakian, Charles D.* University of Rochester Medical School, Rochester, New York.

Forty steroids were studied for their renotrophic, androgenic and thymus-regressing properties by implanting pellets (14 ± mg.) of the compounds subcutaneously into castrated mice and weighing the organs after 30 days of treatment.

There was no parallelism between the renotrophic and androgenic properties. The renotrophic-to-androgenic ratio of the compounds demonstrating marked potencies was as follows: 17-Methyl androstanediol-3α,17α, (1.70); androstanediol-3α,17α (1.48); 17-vinyl testosterone (1.14); 17-ethyl testosterone (1.09); testosterone (0.90); testosterone propionate (0.88); 17-methyl testosterone (0.85); androstanol-17α, one-3 (0.79); normal mice (0.74); androstenedione-3,17 (0.63); testosterone-acetate-3, propionate-17 (0.56). The more potent steroids also were studied in a 10 day period of treatment. The renotrophic-to-androgenic ratio was higher than in the 30 day experiments for all of the steroids but the sequence for the various steroids remained the same.

Is Testosterone Therapy Indicated in Female Patients with Addison's Disease?* *Forbes, Anne P., Edward C. Reifenstein, Jr., Lawrence W. Kinsell* and *Fuller Albright.* From the Department of Medicine of the Harvard Medical School and from the Medical Service of the Massachusetts General Hospital, Boston, Massachusetts.

It is our belief that the androgens arising from the adrenal cortex have an important somatotropic function (anabolism of protoplasm). In Addison's disease all of the hormones of the adrenal are deficient; the loss of the adrenal androgenic steroids reduces the anabolism of protoplasm. This loss is of serious consequence in females since in them the adrenal constitutes the sole source of androgen. Therefore testosterone preparations with their somatotropic properties seem indicated in women with Addison's disease. Complete metabolic studies of nitrogen, phosphorus and calcium in a female patient with Addison's disease before and after testosterone treatment are presented.

Cortin Excretion in Burned Patients.† *Winter, Helen A., Mary Beth Glendening, H. H. Williams, W. E. Abbott, J. W. Hirshfeld* (all by invitation) and *Carl G. Heller.* Departments of Medicine and Surgery, Wayne University College of Medicine, the Medical and Surgical Services of the City of Detroit Receiving Hospital and the Research Laboratories of the Children's Fund of Michigan, Detroit, Michigan.

Urinary cortin excretion has been determined immediately after burns had been sustained in 14 hospitalized patients and repeated determinations were performed at intervals during convalescence. The purpose was to correlate the excretion of cortin, the "S" or sugar hormones of the adrenal cortex, with the nitrogen balance and excretion of other hormones in the burned patients. Twenty-four hour aliquots of urine from a pool collected over a five day metabolic period were ex-

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† The work described in this paper was done under a contract, recommended by the Committee of Medical Research, between the Office of Scientific Research and Development and the Wayne University College of Medicine.

tracted with ethylene dichloride. Nine to ten adrenalectomized rats were given the extracted material orally on each dosage level, and the same number of non-treated adrenalectomized control rats were used for each assay. The survival of the rats subjected to a temperature of 1° C. is used as the index of activity. Results are expressed as "cold units" per 24 hours of urine as defined by Browne. Ten normal control patients excreted 5, 4 or less than 5 or 4 "cold units" per 24 hours. During the first metabolic period 11 patients excreted 20, 30 or more than 20 or 30 "cold units" per 24 hours. The three patients excreting less than 20 "cold units" included a 5-year-old child, an adult woman, and an adult male treated with growth hormone. The 11 patients with elevated cortin excretion continued to excrete large amounts in subsequent periods but this tended to be somewhat lower than in the first period. It is noteworthy that patients with small burns (as little as 8 per cent of the body surface burned) may excrete amounts of cortin as high as encountered in the more severely burned patients. Data on additional patients will be available at the time of presentation.

THE HORMONAL CONTROL OF THE URINARY EXCRETION OF CITRIC ACID. *Shorr, Ephraim, Alice R. Bernheim* and *H. Taussky*. The Russell Sage Institute of Pathology, The Departments of Medicine and Surgery, Cornell University Medical College and the New York Hospital, New York City.

Urinary excretion of citric acid is specifically influenced by steroidal hormones. The excretion curve during the menstrual cycle takes the following pattern: it is lowest at menstruation, rises to a midmenstrual peak approximately at ovulation, is sustained around this higher level until just before the next flow, then falls, generally abruptly to the low menstrual levels. Analysis of this phenomenon by administration of physiological amounts of estrogen, progesterone and testosterone to amenorrheic and post-menopausal subjects showed that: (1) estrogens significantly increase citric acid excretion; (2) progesterone given alone is without effect, but given immediately after estrogen partially sustains the high level previously induced by estrogen; (3) testosterone significantly reduces citric acid excretion. The cyclic variations in urinary citric acid during the menstrual cycle are interpreted as follows: (1) the initial rise during the first half of the cycle is due to increasing elaboration of estrogen by the growing follicle which is maximal at ovulation; (2) the persistence of the higher level during the luteal phase is due to continued estrogen elaboration at lower levels, synergized by progesterone; (3) the premenstrual drop and lower menstrual level are due to sharply reduced elaboration of both hormones, plus the influence of androgens. The significance of this hormonal function is under investigation.

SEXUAL CYCLE AND DIMORPHIC PIGMENTATION IN THE GOLDEN HAMSTER (CRICETUS AURATUS WATERHOUSE). *Kupperman, Herbert S.* (Introduced by: Robert B. Greenblatt). Department of Experimental Medicine, University of Georgia School of Medicine, Augusta, Georgia.

The reproductive cycle of the golden hamster was studied for a period of 18 consecutive months. Cyclic changes in the vagina, as observed by vaginal lavage, occur regularly at four-day intervals throughout the entire year. The proestrous smear in contradistinction to that observed in the rat is composed wholly of cornified cells. Estrus is designated by a thick, white, sticky smear composed predominately of nucleated cells with some cornified cells. This stage is associated in the early phases with receptivity of the female to the male, and somewhat later with post-ovulatory changes in the ovary. The metaestrous smear is characterized by a heavy infiltration of leucocytes associated with a few nucleated and cornified cells. The diestrous smear is indicated by the sparse number of leucocytic and cornified cells present in the smear. Vaginal introitus, although established as early as the 10th–15th day of life, is not indicative of ovarian stimulation. Cyclic changes in

the vagina with corpora lutea formation do not occur until the 33rd–38th day of life and continue, excluding pregnancy, until senility which is observed in animals 500–600 days of age. In the male, spermatogenesis commences on the 35th day of life and continues throughout the year, regardless of season until senility which, as in the female may be observed in animals 500–600 days of age. During the period of testicular activity, a pigmented area of 5–7 mm. in diameter is present on the dorsolateral subcostal region of the skin. The hair in this particular area is coarser than that seen in the rest of the pellage. The pigmented area is either absent or present only to a slight degree, with no difference in hair texture, in the female or castrated male hamster. Pellets of testosterone propionate, implanted subcutaneously, accentuate the degree of pigmentation in the normal male and induce its formation in the castrated male or female or normal female hamster. Pellets of α-estradiol dipropionate caused complete regression of the pigmentation area in the male hamster. The influence of the androgens is indicated further by the fact that the pigmented area, absent in males at birth, appeared with the initiation of testicular function and regressed in senile hamsters.

THE ACTIVITY OF URINARY EXTRACTS ON GLYCOGEN DEPOSITION IN LIVER AND AN IMPROVED METHOD OF ASSAY. *Eggleston, Nancy M., Konrad Dobriner* and *C. P. Rhoads.* Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York City.

The neutral ether-soluble fraction obtained from unhydrolyzed urine of normal and diseased individuals was studied to ascertain whether or not glycogen was deposited or maintained in the livers of adrenalectomized animals following administration of these fractions. The Reinecke-Kendall test using rats was found to detect the presence of 1 rat unit, and with mice, 0.5 rat unit could be determined. When the mice were not fasted prior to the first injection, the sensitivity of the test was increased so that 0.05 rat unit was effective, permitting the performance of a complete assay on a 36- to 48-hour specimen of urine. The technics applied will be described. There was activity in the crude neutral, ketonic and non-ketonic fractions; this finding confirms and extends the observations of Weil and Browne and Venning Hoffman and Browne and of Dorfmann et al. The daily urinary excretion in normal individuals was found to be between 0.5 and 2 rat units. The results of these tests on normal individuals and on patients with cancer and with adrenal cortical syndrome will be discussed.

THE EFFECT OF VITAMIN DEFICIENCIES ON ESTRADIOL INACTIVATION BY LIVER SLICES. *Singher, H. O., Howard C. Taylor, Jr., C. P. Rhoads* and *K. Unna.* Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York City.

Biskind and coworkers have demonstrated an interrelationship between B-complex deficiency and the production of experimental estrus by estradiol, in animals. They also have shown a connection between B-complex therapy and certain gynecological conditions in man. The present paper, in an attempt to find an approach to the enzyme systems involved in estradiol inactivation, deals with the effect of deficiencies of individual known members of the B-complex and vitamin A on the ability of rat and mouse liver slices to inactivate estradiol. Liver slices from riboflavin and thiamin deficient rats are unable to inactivate estradiol under conditions in which controls on the same diet but receiving adequate amounts of these vitamins possess this activity. The ability of liver slices from riboflavin and thiamin deficient animals to inactivate estradiol is a function of the tissue concentration of these vitamins. When rat liver riboflavin values fall below 12γ/gm. wet weight, the slices can no longer inactivate estradiol under experimental conditions. Similarly, when rat liver thiamin values fall below 1γ/gm., the inactivating ability is lost. When riboflavin or thiamin levels are brought back to normal, the reappear-

ance of the inactivating ability follows the rise in concentration of these vitamins. Pyridoxine, pantothenic acid, biotin and vitamin A deficiencies have no effect on estradiol inactivation under the same conditions.

THE EFFECT OF CASTRATION AND VARIOUS STEROIDS ON THE ARGINASE ACTIVITY OF THE TISSUE OF THE MOUSE. *Kochakian, Charles D.*, University of Rochester Medical School, Rochester, New York.

Mice castrated at 16.5–19.5 gm. body weight were implanted subcutaneously one month later with 14 ± 1 mg. pellets of various steroids. Arginase determinations were made 10 and 30 days later. None of the steroids affected the enzyme content of the liver or intestine, but that of the kidneys was markedly increased by many of the steroids and in three instances decreased. The order of change in per cent difference per gram of tissue for the 30-day experiments was: Methyl testosterone, 632; Testosterone, 584; Testosterone propionate, 308; 17-Methyl androstanediol-3α, 17α, 269; Androstanol-17α, one-3, 135; α-estradiol, 88; Androstanediol-3α, 17α, 71; 17-Vinyl testosterone, 55; Testosterone-acetate-3, propionate-17, 35. Eighteen other compounds had no effect and isoandrosterone, 17-methyl androstanediol-3β, 17α and 17-methyl androstanediol-3β, 17α caused decreases of 33 to 39 per cent. The changes were not related to changes in kidney weight or amount of material absorbed. The increases in arginase activity represented greater amounts of enzyme and not a production of arginase activators. The kidneys of the castrated mice contained the same amount of total arginase but greater amounts per gram of tissue than those of the normal mice.

NEUTRAL NON-KETONIC URINARY CHROMOGEN IN THE $SbCl_3$ REACTION.* *Pincus, Gregory*. From the Physiological Laboratories, Clark University, Worcester, Massachusetts.

The non-ketonic, neutral fraction of the ether soluble extract of acid-hydrolized human and guinea pig urines contains material which reacts with $SbCl_3$ to give a typical blue color. The chromogen is excreted by human subjects in minimum amount at night and there is a diurnal rhythm of output markedly similar to that described for the urinary 17-ketosteroids. The amount of chromogen increases markedly in guinea-pig urines after the injection of certain androgenic and corticoid steroids. The probable steroid nature of the urinary chromogen will be indicated, and its role as an indicator of phases of steroid metabolism discussed.

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REVISED BY-LAWS
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ASSOCIATION NOTICE

At the Twenty-seventh Annual Meeting of the Association in Chicago, June 12 and 13, 1944, the following revision of the By-Laws[1] of the Society was recommended by the Council and was adopted by the members at the annual business session.

THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS BY-LAWS

Article I—Name and Object

The name and object of this Association shall be as set forth in the Articles of Incorporation. The organization shall be conducted for scientific purposes, for the advancement and promulgation of knowledge regarding the internal secretions and for the facilitation of personal relationship among investigators in the subject of endocrinology.

Article II—Membership

Section 1. The Association shall consist of active members only. Of these, there shall be two classes, annual members and life members.

Section 2. Eligibility: Any qualified physician or biologist in good professional standing shall be eligible for nomination to annual membership. Annual members of high professional standing may, upon invitation by the Council, become life members upon payment of one hundred dollars, which sum shall be in lieu of annual membership assessments.

Section 3. Nomination and Election: Nominations for membership shall be made and seconded by members of the Association on blanks furnished by the Secretary, and shall be submitted to the Council. The Council shall determine eligibility and shall vote by ballot upon nominations. A majority of votes cast shall constitute election.

Section 4. Resignation, Forfeiture and Expulsion: The resignation of any member in good standing may be accepted at any annual meeting of the Council, providing his dues have been paid in full for the current year.

Any member whose annual assessment is in arrears one month after the sending of a second notice to his last known address shall automatically

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[1] The Constitution of the Association comprises the Articles of Incorporation, as set forth in the certificate recorded with the Secretary of State of the State of Delaware on January 31, 1918.

These Articles of Incorporation grant broad powers to the Association; give it perpetual existence; exempt entirely the private property of members for the payment of corporate debts; specify the general qualifications for membership; and authorize the Society to make and alter By-Laws for the regulation of its activities.

forfeit his membership. Delinquent members may be reinstated by the Council, providing all indebtedness to the Association is discharged.

Upon the recommendation of the Council, any member may be expelled by a majority vote of the members present at an annual meeting of the Association, provided that a copy of the charges against the member in question and a notice of hearing thereon by the Council shall have been given him at least thirty days before the annual meeting.

Article III—Meetings and Quorum

Section 1. Annual: The annual meeting of the Association shall be held at such time and place as shall be determined by the Council.

Section 2. Special: Regional branches of the Association may be authorized by the Council, upon petition by ten members. These may hold special scientific meetings as desired and elect their own officers.

Section 3. Quorum: Fifteen members shall constitute a quorum for the transaction of business at any annual meeting.

Section 4. Council Meetings: At least one meeting of the Council shall be held at each annual meeting of the Association. In the interval between annual meetings the President may on his own volition or at the request of two members submit questions by mail to the members of the Council for their consideration and decision.

Article IV—Officials

Section 1. Officers: The officers shall be a President, a President-Elect, a Vice-President and a Secretary-Treasurer, who shall be elected annually for a term of one year by the members of the Association. The officers shall enter upon their duties at the close of the annual meeting at which they are elected. The powers and duties of the officers shall be such as usually devolve upon their respective positions.

Section 2. Council: The officers so elected and nine additional members, three of whom shall be elected at each annual meeting, shall constitute the Board of Directors of the Corporation and shall be known as the Council. The term of office of members of the Council shall be three years. The President of the Association shall be ex-officio the Chairman of the Council. The Secretary-Treasurer shall be ex-officio the Secretary of the Council.

Section 3. Powers: The general management of the Association shall be vested in the Council. It shall regularly perform the ordinary duties of a board of directors of a corporation and shall possess all the powers conferred upon the directors by the Charter of Incorporation. The Council shall have power at any time to appoint any committee it may deem necessary and to delegate whatever powers necessary to such committees.

Article V—Nomination of Officers

Section 1. Nominating Committee: The Nominating Committee shall consist of three members appointed for the ensuing year by the newly-elected President and accepted by the Council. The President shall designate one member to be Chairman of the Nominating Committee.

Section 2. Nomination of Officials: A) The Nominating Committee shall make at least one nomination for each of the four offices and for each of the positions on the Council to be filled by vote of the members. Any member of the Association may submit nominations to the Nominating Committee

for its consideration. B) The nominations of the Nominating Committee shall be transmitted to the Secretary at least sixty days before the annual meeting at which they are to be considered. C) The Secretary shall send to each member, at least four weeks before the annual meeting, a printed ballot containing the list of nominees and space for such additional names as the member wishes to propose, and at the same time shall notify the members that they may vote by mail by returning the marked ballot to the Secretary before the beginning of the business session at which the elections are to take place.

Section 3. Elections: At the annual meeting the Secretary shall present to the Tellers, appointed by the President, the ballots submitted by the members. The Tellers shall count the votes and announce the results at the business session. A majority of votes cast shall be necessary to elect an official. In case no candidate shall have received a majority of votes, the office in question shall be filled by majority vote of those members present at the business session.

Section 4. Filling of Vacancies: The Council shall fill all vacancies in elective positions except such as occur at an annual meeting of the Association.

Article VI—Financial

Section 1. Dues: The dues shall be the annual cost of subscription to Endocrinology for members, which shall be determined by majority vote at the annual meeting, upon recommendation by the Council.

Section 2. Expenditures: No expenditures from the general funds of the Association except those required in the performance of the ordinary duties of officers shall be made except by vote of the Society or the Council.

Article VII—Publications

Section 1. The official organs of publication of the Association shall be the bulletin Endocrinology and such other periodicals or books as from time to time the Association may authorize. Ownership of these shall be vested in the Association.

Article VIII—Papers at Scientific Sessions

The President and Secretary shall be authorized to arrange programs for the scientific sessions at the annual meeting. The manner of selection of papers to be presented and the time allowed for presentation shall be determined by the Council.

Article IX—Changes in By-Laws

Section 1. These By-Laws, after having been approved by the Council and adopted by the Association, may be amended at any annual meeting as hereinafter provided.

Proposed amendments to the By-Laws must be sent to the Secretary at least four weeks before the date of the annual meeting at which they are to be considered. The Secretary shall promptly transmit them to the members of the Council. At the annual meeting the Council shall consider the proposed amendments and make recommendations to the members at the business meeting of the Association. A majority of the votes of members at the business session of the annual meeting shall be necessary for adoption of an amendment.

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